anticipated by Chen, *et al.* (*Proc. Nat. Acad. Sci. USA* 88:11368-11372 (1991)) in view of Andres, *et al.* (*J. Biol. Chem.* 268(2):1383-1390 (1993)). Finally, claims 9-13 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Moosmann, *et al.* (*Nucl. Acids Res.* 24(6):1171-1172 (1996)), Severne, *et al.* (*EMBO J.* 7(8):2503-2508 (1988)), Baskar, *et al.* (*J. Virology* 70(5):3207-3214 (1996)), Choi, *et al.* (*Molec. Cell Biol.* 11(6):3070-3074 (1991)) and Jang, *et al.* (*Enzyme* 44(1-4):292-309 (1990)). For the reasons set forth herein, each of the foregoing rejections is overcome.

STATUS OF THE CLAIMS

Claims 1-14 are pending in the above-referenced patent application and are currently under examination. New claims 15-19 have been added and are presented for examination. Support for newly added claims 15-19 can be found throughout the specification and in the claims as originally filed and, thus, no new matter has been introduced. Applicants acknowledge, with appreciation, the Examiner's indication that claims 1-8 and 14 are free of the prior art.

Claim 1 has been amended to overcome the Examiner's concern that the claim presently on file is indefinite. More particularly, in order to expedite prosecution, the preamble and last subparagraph of claim 1 have been amended to more particularly set forth that the claimed method is a method for screening rather than obtaining or characterizing a promoter or gene. Support for this screening method is found throughout the description, for example at page 13, lines 30-32 and is implicit in the entire description of the claimed method. In addition, claim 1 has been amended for the sake of clarity to refer to first and second DNA constructs, rather than to "sequences." Claim 1 has also been amended for consistency with the claims amended in accordance with the Examiner's suggestion that a limitation be added setting forth that a coding sequence in a construct not be operably linked to an expression (transcription) control element. As such, claim 1 has been amended to indicate that the coding sequence in the second construct is not so linked, rather than stating that the second construct "lacks a promoter."

Dependent claim 6 has been amended for the sake of clarity so that it is consistent with amended claim 1.

Claims 7 and 8 have been canceled in favor of newly added claims 18 and 19. Claim 18 is based on claim 7, but is now an independent claim directed to a method for obtaining tissue or specialized cells comprising a detectable indicator associated with a target gene having restricted expression. Whereas method claim 7 incorporated steps by reference to claim 1, new claim 18 specifically recites the first three steps of claim 1 and additionally recites the selection of tissue or specialized cells containing the detectable indicator.

New claim 19 is based on claim 8 which was directed to a method of obtaining a mammal from a transformed ES cell. However, in order to expedite prosecution of the present case, claim 19 specifically recites that the mammal obtained is a mouse or pig, that the method includes the first two steps recited in claim 1 and further recites the steps suggested by the Examiner as being necessary for the claim to be concordant with the purpose set out in the preamble.

Claim 9 has been amended in accordance with the Examiner's suggestion to incorporate the limitation of claim 11 and to specify that the sequence is not operably linked to an expression (transcription) control element. In view of the amendment to claim 9, claim 11 has been canceled without prejudice or disclaimer.

Claim 10 has been canceled, without prejudice or disclaimer, in view of newly added claim 15 in which the limitations of claims 9 and 10 have been combined. New claim 15 further recites that the coding sequence not be operably linked to a transcription control element, as is the case for amended claim 9.

Claim 12 has been amended to specify that the coding sequence in the DNA construct having the splice acceptor is not operably linked to a transcription control element, as suggested by the Examiner.

Newly added claims 16 and 17 are dependent from claim 1 and recite the embodiment of the invention described at page 21, lines 20-34 and in Example 3 set out at page 37 of the description. Briefly, the first indicator component is not transcribed until an intervening sequence is removed by a recombinase acting as the second indicator component.

Expression of the second indicator component in a cell in which the first indicator component is capable of expression driven by the promoter having restricted expression results in the first indicator component being expressed. New claim 17 provides further features as described in Example 3.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 7-14 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. In making this rejection, the Examiner has alleged that claims 7 and 8 are only enabled for a mouse.

Applicants respectfully disagree. However, in order to expedite prosecution of the present case, claim 8 has been canceled and new claim 19 has been added which is limited to the production of a mouse or pig from an ES cell. It is respectfully submitted that the Examiner has overlooked the fact that the state of the art with respect to ES cells went beyond the use of murine ES cells and includes, *inter alia*, the use of porcine ES cells. For instance, United States Patent No. 5,523,226 describes the culturing and transformation of porcine ES cells and production of transgenic swine (*see, e.g.*, page 23, lines 5-7 of the specification). A copy of United States Patent No. 5,523,226 is enclosed for reference by the Examiner.

Moreover, it is respectfully pointed out that the present invention is not limited to the use of transformed ES cells. As is set out in the description, the present invention provides a method of obtaining specialized cells or tissues comprising a detectable indictor associated with a target gene having restricted expression (*see, e.g.*, page 15, lines 18-35; page 23, lines 12-25; and the Examples). Consequently, claim 7 has been canceled and new claim 18 has been added which is directed to a method of obtaining such tissue or specialized cells. Claim 18 is based on claim 1 and therefore, appears to be free from the concerns the Examiner had with claim 7 based on 35 U.S.C. § 112, first paragraph. Clearly, it is known from the art that a wide variety of eukaryotic cells can be transformed and made to differentiate into tissue or specialized cells, even as complete organisms. As such, this methodology is routine and does not rely upon the culturing of ES cells. Further, germ-line transmission is not required for

the simple production of specialized cells, tissue or organisms comprising specialized cells or tissue.

Claims 9-14 stand rejected as allegedly not being enabling for identifying promoters or genes. However, in the Office Action, the Examiner has indicated that this rejection can be overcome by amending the claims to recite a DNA construct in which the second indicator component is not operably linked to a promoter, or not operably linked to an expression control sequence (*see*, the claim rejection under 35 U.S.C. § 103). As such, in order to expedite prosecution, the claims have been amended so that all of the claims reciting the construct containing the second indicator component indicate that the coding sequence for the component is not "operably linked to a transcription control element." This claim language is consistent with the description set forth in the specification (*see, e.g.*, the specification at page 13, lines 30-32).

In view of the amendments to the claims and the foregoing remarks, Applicants respectfully submit that the Examiner's concerns have been overcome. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-5 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the method steps are not concordant with the purpose set forth in the preamble. However, in the Office Action, the Examiner has indicated that this rejection can be overcome by amending the claims to recite steps for obtaining and characterizing a promoter or a gene. However, it is noted that the use of "detecting" in claim 1 was intended to describe a method in which DNA flanking the insert is necessarily isolated or further characterized. Accordingly, claim 1 has been amended to make it clear that the method is directed to screening. For the sake of clarity, the screening is defined as the integration of the second DNA construct into a gene having restricted expression. As explained above, claim 6 has been amended to be consistent with the amendments made to claim 1. In view of the amendments to claims 1 and 6, it appears that the Examiner's concerns regarding claims 1-5 have been overcome.

Claims 7 and 8 stand rejected as allegedly being indefinite for not reciting steps describing how a transfected cell is grown into an organism. However, in the Office Action, the Examiner has indicated that this rejection could be overcome by reciting such steps. As explained above, in order to expedite prosecution, claims 7 and 8 have been canceled and new claims 18 and 19 have been added. New claim 19 is now the only claim reciting the production of an organism. Claim 19 incorporates the missing steps suggested by the Examiner and, therefore, appears to be free of the objection.

In view of the amendments to the clams and the foregoing remarks, Applicants respectfully submit that the Examiner's concerns have been overcome. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, second paragraph.

REJECTION UNDER 35 U.S.C. § 102(B)

Claim 9 was rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chen, *et al.* (*Proc. Nat. Acad. Sci. USA* 88:11368-11372 (1991)) in view of Andres, *et al.* (*J. Biol. Chem.* 268(2):1383-1390 (1993)).

For a rejection of claims under § 102(b) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . ***There must be no difference between the claimed invention and the reference disclosure***, as viewed by a person of ordinary skill in the field of the invention.

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

In order to expedite prosecution of the present case, the limitations of claim 11 have been incorporated into amended claim 9, and the limitation of claim 10 has been incorporated into newly added claim 15. Applicants respectfully submit that neither Chen, *et al.* nor Andres, *et al.* teach ***all*** of the elements, features or limitations of claims 9 and 15 and, thus, they cannot form the basis for a proper anticipation rejection.

In view of the amendment to claim 9 and newly added claim 15, Applicants respectfully submit that claims 9 and 15 are not anticipated by Chen, *et al.* in view of Andres, *et al.* Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 102(b).

REJECTION UNDER 35 U.S.C. § 103

claims 9-13 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Moosmann, *et al.* (*Nucl. Acids Res.* 24(6):1171-1172 (1996)), Severne, *et al.* (*EMBO J.* 7(8):2503-2508 (1988)), Baskar, *et al.* (*J. Virology* 70(5):3207-3214 (1996)), Choi, *et al.* (*Molec. Cell Biol.* 11(6):3070-3074 (1991)) and Jang, *et al.* (*Enzyme* 44(1-4):292-309 (1990)). However, in the Office Action, the Examiner has indicated that this rejection can be overcome by incorporating the limitation that the sequence encoding the second indicator component is not operably linked to an expression control sequence (*see*, page 9 of the Office Action). As such, in order to expedite prosecution, all of the pertinent claims have been amended to more specifically recite that the DNA (or sequence) encoding the second indicator component is not operably linked to a transcription control element. As explained above, support for this amendment can be found throughout the specification as originally filed and, thus, no new matter has been introduced.

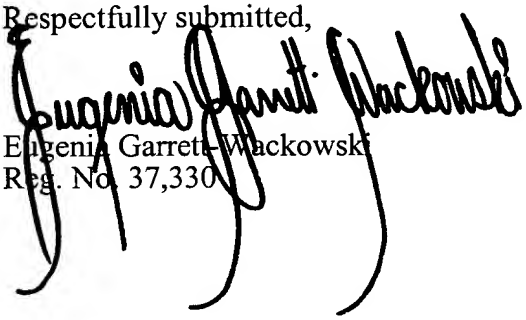
In view of the amendment to the claims, Applicants respectfully submit that claims are not obvious over the cited references. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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